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24239 7590 10/03/2007 MOORE & VAN ALLEN PLLC P.O. BOX 13706 Research Triangle Park, NC 27709			EXAMINER BAUGHMAN, MOLLY E	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/536,502	Applicant(s) GEDDES ET AL.	
	Examiner Molly E. Baughman	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-27 and 38-49 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-27 and 38-49 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 May 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>See Continuation Sheet</u> . | 6) <input type="checkbox"/> Other: ____ |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :6/28/07;
10/30/06; 10/30/06; 5/19/06.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 5/19/06 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. It is noted that citation No. 2 and 3 have fully been considered, however, have been lined through to avoid duplicate reference listings at time of print.

Claim Objections

1. Claim 2 is objected to because of the following informalities: The claim depends from itself. Appropriate correction is required.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Claims 1, 2, 5-10, 12-13, 16, 20-26, 38-39, 41-44, and 46-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Vo-Dinh (US 5,814,516).

Regarding claims 1, Vo-Dinh teaches a method for detecting a target pathogen in a sample, the method comprising: a) providing a system comprising: a layer of immobilized metal particles positioned on a surface substrate, wherein the immobilized metal particles have attached thereto a captured biomolecular probe with an affinity for the target pathogen; b) contacting the sample with the immobilized biomolecular probes, wherein the target pathogen binds to the immobilized biomolecular probes; and c) contacting the bound target pathogen with a free biomolecular probe, wherein the free biomolecular probe has an affinity for the target pathogen and has attached thereto a fluorophore, and wherein binding of the free biomolecular probe to the target pathogen causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission when excited by an irradiating source (col.3, lines 48-67 - col.4, lines 1-11; col.6, lines 5-41).

Regarding claim 2, Vo-Dinh teaches the method wherein the immobilized and free biomolecular probes comprise a DNA sequence complementary to a target pathogen DNA sequence (col.6, lines 42-55).

Regarding claim 5, Vo-Dinh teaches the method wherein the metal particles is silver or gold (col.8, lines 15-18; col.12, lines 29-30).

Regarding claims 6-7, Vo-Dinh teaches the method further comprising detecting fluorescence emission with a detection device, wherein the detection device comprises

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a spectrometer, luminometer microscope, plate reader, fluorescent scanner, flow cytometer, or any combination thereof (col.8, lines 50-67; col.9, lines 1-3).

Regarding claim 8, Vo-Dinh teaches the method wherein the immobilized biomolecular probe is covalently linked to the immobilized metallized particles (col.8, lines 15-18).

Regarding claim 9, Vo-Dinh teaches the method wherein binding of the immobilized and free DNA sequence complementary to the target pathogen DNA is conducted under high stringent hybridization conditions (col.10, lines 50-55).

Regarding claim 10, Vo-Dinh teaches the method wherein the irradiating source uses a 1-photon or 2-photon excitation means (col.9, lines 8-15).

Regarding claims 12-13, Vo-Dinh teaches the method wherein the fluorophore comprises a low quantum yield species and can undergo two-photon excitation (col.6, lines 62-65).

Regarding claim 16, Vo-Dinh teaches an assay method for detecting a target pathogen in a sample, the method comprising: a) providing a system comprising: an immobilized metallized layer positioned on a surface substrate, wherein the immobilized metallized layer has attached thereto an immobilized capture DNA sequence probe complementary to a known DNA sequence of the target pathogen; b) contacting the sample with the immobilized capture DNA sequence probe, wherein the DNA sequence of the target pathogen binds to the immobilized capture DNA sequence probe; c) contacting the bound DNA sequence of the target pathogen with a free capture DNA sequence probe, wherein the free capture DNA sequence probe is complementary to a

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known DNA sequence of the target pathogen, wherein the free capture DNA sequence probe has attached thereto a fluorophore, wherein binding of the free capture DNA sequence probe to the DNA sequence of the target pathogen causes the fluorophore to be positioned a sufficient distance from the immobilized metallized surface to enhance fluorescence emission when excited by an irradiating source; and d) identifying the target pathogen by fluorescence emission by irradiating the system with an irradiating source to excite the fluorophore (col.3, lines 48-67 - col.4, lines 1-11; col.6, lines 5-55).

Regarding claim 20, Vo-Dinh teaches the method of claim 16 wherein the metallized surface comprises metal particles comprising silver or gold (col.8, lines 15-18; col.12, lines 29-30).

Regarding claims 21-22, Vo-Dinh teaches the method of claim 16, further comprising detecting fluorescence emission with a detection device, wherein the detection device comprises a spectrometer, luminometer microscope, plate reader, fluorescent scanner, flow cytometer, or any combination thereof (col.8, lines 50-67; col.9, lines 1-3).

Regarding claim 23, Vo-Dinh teaches the method of claim 16, wherein binding of the immobilized and free capture DNA sequence complementary to the target pathogen DNA is conducted under high stringent hybridization conditions.

Regarding claim 24, Vo-Dinh teaches the method of claim 16, wherein the irradiating source uses a 1-photon or 2-photon excitation means (col.9, lines 8-15).

Regarding claims 25-26, Vo-Dinh teaches the method of claim 16, wherein the fluorophore comprises a low quantum yield species and can undergo two-photon excitation (col.6, lines 62-65).

Regarding claim 38, Vo-Dinh teaches an assay system for detecting a target pathogen comprising: a layer of immobilized metal particles deposited on a surface substrate, wherein a captured biomolecular probe having an affinity for a target pathogen is immobilized on the metal particles; a free biomolecular probe having an affinity for a target pathogen, wherein the free biomolecular probe has attached thereto a fluorophore; wherein binding of the immobilized and free biomolecular probe to the target pathogen causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission (col.3, lines 48-67 - col.4, lines 1-11).

Regarding claim 39, Vo-Dinh teaches the system according to claim 38, wherein the immobilized and free biomolecular probes comprise a DNA sequence complementary to a target pathogen DNA sequence (col.6, lines 42-55).

Regarding claim 41, Vo-Dinh teaches the system according to claim 38, wherein the metal particles is silver or gold (col.8, lines 15-18; col.12, lines 29-30).

Regarding claims 42-43, Vo-Dinh teaches the system according to claim 38, further comprising a detection device for detecting fluorescence emission, wherein the detection device comprises a spectrometer, luminometer microscope, plate reader, fluorescent scanner, flow cytometer, or any combination thereof (col.8, lines 50-67; col.9, lines 1-3).

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Regarding claim 44, Vo-Dinh teaches the system according to claim 38 further comprising an irradiating source (col.9, lines 8-15).

Regarding claims 46-47, Vo-Dinh teaches the system according to claim 38, wherein the fluorophore comprises a low quantum yield species, and can undergo two-photon excitation (col.6, lines 62-65).

3. Claims 1, 4-8, 10-14, 38, and 41-48 are rejected under 35 U.S.C. 102(e) as being anticipated by anticipated by Lakowicz (US 2002/0160400 A1).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Regarding claim 1, Lakowicz teaches a method for detecting a target pathogen in a sample, the method comprising: a) providing a system comprising: a layer of immobilized metal particles positioned on a surface substrate, wherein the immobilized metal particles have attached thereto a captured biomolecular probe with an affinity for the target pathogen; b) contacting the sample with the immobilized biomolecular probes, wherein the target pathogen binds to the immobilized biomolecular probes; and c) contacting the bound target pathogen with a free biomolecular probe, wherein the free biomolecular probe has an affinity for the target pathogen and has attached thereto a

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fluorophore, and wherein binding of the free biomolecular probe to the target pathogen causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission when excited by an irradiating source (Figure 35, pg.1-2 [0013]; pg.16 [0158]).

Regarding claim 4, Lakowicz teaches the method wherein the fluorophore is positioned from about 50 to about 500 Angstroms from the immobilized metal particles after the free biomolecular probe contacts the target pathogen (pg.5 [0071]).

Regarding claim 5, Lakowicz teaches the method wherein the metal particles is silver or gold (pg.3 [0060]).

Regarding claims 6-7, Lakowicz teaches the method further comprising detecting fluorescence emission with a detection device, wherein the detection device comprises a spectrometer, luminometer microscope, plate reader, fluorescent scanner, flow cytometer, or any combination thereof (col.5 [0077]).

Regarding claim 8, Lakowicz teaches the method wherein the immobilized biomolecular probe is covalently linked to the immobilized metallized particles (pg.5 [0072]).

Regarding claim 10, Lakowicz teaches the method wherein the irradiating source uses a 1-photon or 2- photon excitation means (col.5 [0077]).

Regarding claim 11, Lakowicz teaches the method wherein the biomolecular probe is an antibody and the target pathogen is an antigen (Figure 35).

Regarding claims 12-13, Lakowicz teaches the method wherein the fluorophore comprises a low quantum yield species and can undergo two-photon excitation (pg.4 [0066], [0070]).

Regarding claim 14, Lakowicz teaches the method, wherein the fluorophore comprises Rhodamine B, rose bengal or fluorescein isothiocyanate (pg.4 [0066]).

Regarding claim 38, Lakowicz teaches an assay system for detecting a target pathogen comprising: a layer of immobilized metal particles deposited on a surface substrate, wherein a captured biomolecular probe having an affinity for a target pathogen is immobilized on the metal particles; a free biomolecular probe having an affinity for a target pathogen, wherein the free biomolecular probe has attached thereto a fluorophore; wherein binding of the immobilized and free biomolecular probe to the target pathogen causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission (Figure 35; pg.1-2).

Regarding claim 41, Lakowicz teaches the system according to claim 38, wherein the metal particles is silver or gold ((pg.3 [0060]).

Regarding claims 42-43, Lakowicz teaches the system according to claim 38, further comprising a detection device for detecting fluorescence emission, wherein the detection device comprises a spectrometer, luminometer microscope, plate reader, fluorescent scanner, flow cytometer, or any combination thereof (col.5 [0077]).

Regarding claim 44, Lakowicz teaches the system according to claim 38 further comprising an irradiating source (col.5 [0077]).

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Regarding claim 45, Lakowicz teaches the system according to claim 38, wherein the biomolecular probe is an antibody and the target pathogen is an antigen (Figure 35).

Regarding claims 46-47, Lakowicz teaches the system according to claim 38, wherein the fluorophore comprises a low quantum yield species, and can undergo two-photon excitation (pg.4 [0066], [0070]).

Regarding claim 48, Lakowicz teaches the system according to claim 38, wherein the fluorophore comprises Rhodamine B, rose bengal or fluorescein isothiocyanate (pg.4 [0066]).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 5-7, 11-14, 38, 41-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carron et al. (US 6,770,488 B1).

Regarding claims 1, Carron teaches a method for detecting an antigen, the method comprising: a) providing a system comprising: a layer of immobilized metal particles positioned on a surface substrate, wherein the immobilized metal particles have attached thereto a captured biomolecular probe (i.e. an antibody) with an affinity for the antigen; b) contacting the sample with the immobilized biomolecular probes, wherein the antigen binds to the immobilized biomolecular probes; and c) contacting the bound antigen with a free biomolecular probe, wherein the free biomolecular probe has an affinity for the antigen and has attached thereto a fluorophore, and wherein binding of the free biomolecular probe to the antigen causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission when excited by an irradiating source (Figure 5; col.5, lines 39-44; col.10, lines 7-11).

Regarding claim 5, Carron teaches the method wherein the metal particles is silver or gold (col.7, "Colloids", specifically lines 51-52).

Regarding claims 6-7, Carron teaches the method further comprising detecting fluorescence emission with a detection device, wherein the detection device comprises a spectrometer, luminometer microscope, plate reader, fluorescent scanner, flow cytometer, or any combination thereof (col.14, lines 50-67; col.15, lines 6-11).

Regarding claim 11, Carron teaches the method wherein the biomolecular probe is an antibody and the target is an antigen (Figure 5; col.14, lines 19-21).

Regarding claims 12-13, Carron teaches the method wherein the fluorophore comprises a low quantum yield species and can undergo two-photon excitation (Example 5, lines 25-30).

Regarding claim 14, Carron teaches the method, wherein the fluorophore comprises Rhodamine B, rose bengal or fluorescein isothiocyanate (Example 5, lines 25-30).

Regarding claim 38, Carron teaches an assay system for detecting an antigen comprising: a layer of immobilized metal particles deposited on a surface substrate, wherein a captured biomolecular probe having an affinity for an antigen is immobilized on the metal particles; a free biomolecular probe having an affinity for an antigen, wherein the free biomolecular probe has attached thereto a fluorophore; wherein binding of the immobilized and free biomolecular probe to the antigen causes the fluorophore to be positioned a sufficient distance from the immobilized metal particles to enhance fluorescence emission (Figure 5; col.5, lines 39-44; col.10, lines 7-11; col.7, "Colloids", specifically lines 51-52; col.14, lines 50-67; col.15, lines 6-11).

Regarding claim 41, Carron teaches the system according to claim 38, wherein the metal particles is silver or gold (col.7, "Colloids", specifically lines 51-52).

Regarding claims 42-43, Carron teaches the system according to claim 38, further comprising a detection device for detecting fluorescence emission, wherein the detection device comprises a spectrometer, luminometer microscope, plate reader,

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fluorescent scanner, flow cytometer, or any combination thereof (col.14, lines 50-67; col.15, lines 6-11).

Regarding claim 44, Carron teaches the system according to claim 38 further comprising an irradiating source (col.14, lines 50-67; col.15, lines 6-11).

Regarding claim 45, Carron teaches the system according to claim 38, wherein the biomolecular probe is an antibody and the target is an antigen (Figure 5).

Regarding claims 46-47, Carron teaches the system according to claim 38, wherein the fluorophore comprises a low quantum yield species, and can undergo two-photon excitation (Example 5, lines 25-30).

Regarding claim 48, Carron teaches the system according to claim 38, wherein the fluorophore comprises Rhodamine B, rose bengal or fluorescein isothiocyanate (Example 5, lines 25-30).

While Carron teaches the general method and assay system utilizing an antibody, antigen and a dye tagged reporter, he doesn't specifically disclose detecting particular targets, or more specifically, target pathogens, during his method.

One of ordinary skill in the art would have been motivated to modify the method and assay system of Carron et al. to incorporate a target pathogen as the antigen because it was conventional in the art at the time of the invention to detect various pathogens using various methods and assays systems and one of skill in the art could have also used the method and assay system for detecting various pathogens. Therefore skilled artisan would have had a reasonable expectation of success in detecting target pathogens as the antigens in the method of Carron et al. It would have

been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed target pathogen therein.

7. Claims 4, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carron et al. (US 6,770,488 B1) as applied to claims 1, 5-7, 11-14, 38, 41-48, and further in view of Lakowicz, "Radiative Decay Engineering: Biophysical and Biomedical Applications," Analytical Biochemistry, 2001, Vol.298, pp.1-24.

The teachings of Carron are discussed above. This reference is silent regarding the positioning of the fluorophore from the immobilized metal particles in the method.

Lakowicz also discusses systems of the same method and apparatus, wherein technology based on surface enhanced energy transfer comprising metal particles, and low quantum yield fluorophores is used in antibody-antigen sandwich immunoassays (pg.17, "Assays Based on Low Quantum Yield Fluorophores" and Figure 27). He also notes that distances between 50-200 Angstroms from the metal surfaces are optimal for enhancing the emission of fluorescence (pg.8, 2nd column and Figure 10).

One of ordinary skill in the art would have been motivated to modify the method and assay system of Carron et al. to position the fluorophore 50 to 500 Angstroms from the metal particles because Lakowicz demonstrates the benefits of positioning fluorophores between 50 to 200 Angstroms from the metal surface in technology used in immunoassays which involve antigen-antibody interactions, as he states that "enhanced field and increased radiative rates occur at longer distances from the metal than quenching" (pg.8, 2nd column). Therefore, the skilled artisan would have had a

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reasonable expectation of success in positioning the fluorophore 50 to 500 Angstroms from the metal particles in the method and assay system of Carron et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed distance therein.

8. Claims 3, 15, 17-18, 40 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carron et al. (US 6,770,488 B1) as applied to claims 1, 5-7, 11-14, 38, 41-48, and further in view of Cao et al., "Nanoparticles within Raman Spectroscopic Fingerprints for DNA and RNA Detection," Science, Aug.2002, Vol.297, pp.1536-1540.

The teachings of Carron are discussed above. Carron does not discuss the method or assay system wherein the antigen is *B. anthracis* [claims 3, 18, and 40]. He also does not discuss the method or assay system wherein the free biomolecular probe further comprises a metal colloid attached thereto and positioned for sandwiching the fluorophore between the metal colloid and immobilized metal particles on the substrate when the target pathogen is bound [claims 15, 17, and 49].

Cao et al. discuss a method using surface-enhanced Raman Scattering (SERS) wherein capture oligonucleotides are bound to a chip, hybridized with a target sequence and a detection probe comprising a fluorophore and a metal colloid (i.e. Au nanoparticle), wherein the fluorophore is sandwiched between the chip surface and the nanoparticle (see Figure 1 and pg.1537, left column). The chip with immobilized complex is immediately treated with an Ag enhancement solution. Although Cao does not discuss the method and assay system wherein the capture oligonucleotides are

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immobilized on metal particles, he demonstrates that the nanoparticle/fluorescent probes can be enhanced by metal particles surrounding the complex and therefore, demonstrates the concept of sandwiching a fluorescent label between a metal particle and a metal colloid. Cao also discusses the method wherein the target pathogen is *B. anthracis* (pg.1838, left column).

One of ordinary skill in the art would have been motivated to modify the method and assay system of Carron et al. to detect *B. anthracis* and further include a metal colloid attached to the free biomolecular probe because Cao et al. demonstrates that metal colloids (i.e. nanoparticles) are useful in signal enhancement of SERS assays and allow for the detection of multiple targets in one assay (pg.1537), and further demonstrates the benefits of using such assays to detect *B. anthracis*. The skilled artisan would have had a reasonable expectation of success in detecting *B. anthracis* and further including a metal colloid attached to the free biomolecular probe in the method of Carron et al. for signal enhancement and multiplexing capabilities. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed *B. anthracis* detection and metal colloid therein.

9. Claims 4, 11, 19, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh (US 5,814,516) in view of Lakowicz, "Radiative Decay Engineering: Biophysical and Biomedical Applications," Analytical Biochemistry, 2001, Vol.298, pp.1-24.

The teachings of Vo-Dinh are discussed above. This reference is silent regarding the positioning of the fluorophore from the immobilized metal particles in the method [i.e. claims 4 and 19]. This reference also does not discuss the method or assay system wherein the biomolecular probe is an antibody and the target pathogen is an antigen [i.e. claims 11 and 45].

Lakowicz also discusses systems of the same method and apparatus, wherein he demonstrates that technology based on surface enhanced energy transfer comprising metal particles, and low quantum yield fluorophores can also be used in antibody-antigen sandwich immunoassays (pg.17, "Assays Based on Low Quantum Yield Fluorophores" and Figure 27). He also notes that distances between 50-200 Angstroms from the metal surfaces are optimal for enhancing the emission of fluorescence (pg.8, 2nd column and Figure 10).

One of ordinary skill in the art would have been motivated to modify the method of Vo-Dinh et al. to position the fluorophore 50 to 500 Angstroms from the metal particles, as well as use the method and assay system for antigen-antibody binding because Lakowicz demonstrates that such technology can be used in immunoassays which involve antigen-antibody interactions, as well as demonstrates the benefits of positioning fluorophores between 50 to 200 Angstroms from the metal surface, as he states that "enhanced field and increased radiative rates occur at longer distances from the metal than quenching" (pg.8, 2nd column). Therefore, the skilled artisan would have had a reasonable expectation of success in positioning the fluorophore 50 to 500 Angstroms from the metal particles, as well as use antigen-antibody binding in the

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method and assay system of Vo-Dinh et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed distance and antigen-antibody binding therein.

10. Claims 3, 15, 17-18, 40 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh (US 5,814,516) in view of Cao et al., "Nanoparticles within Raman Spectroscopic Fingerprints for DNA and RNA Detection," Science, Aug.2002, Vol.297, pp.1536-1540.

The teachings of Vo-Dinh are discussed above. Although Vo-Dinh discusses the method or assay system wherein the target pathogen is various microorganisms (col.6, lines 5-40), he does not discuss the method or assay system wherein the target pathogen is *B. anthracis* [claims 3, 18, and 40]. He also does not discuss the method or assay system wherein the free biomolecular probe further comprises a metal colloid attached thereto and positioned for sandwiching the fluorophore between the metal colloid and immobilized metal particles on the substrate when the target pathogen is bound [claims 15, 17, and 49].

Cao et al. discuss a method using surface-enhanced Raman Scattering (SERS) wherein capture oligonucleotides are bound to a chip, hybridized with a target sequence and a detection probe comprising a fluorophore and a metal colloid (i.e. Au nanoparticle), wherein the fluorophore is sandwiched between the chip surface and the nanoparticle (see Figure 1 and pg.1537, left column). The chip with immobilized complex is immediately treated with an Ag enhancement solution. Although Cao does

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not discuss the method and assay system wherein the capture oligonucleotides are immobilized on metal particles, he demonstrates that the nanoparticle/fluorescent probes can be enhanced by metal particles surrounding the complex and therefore, demonstrates the concept of sandwiching a fluorescent label between a metal particle and a metal colloid. Cao also discusses the method wherein the target pathogen is *B. anthracis* (pg.1838, left column).

One of ordinary skill in the art would have been motivated to modify the method and assay system of Vo-Dinh et al. to detect *B. anthracis* and further include a metal colloid attached to the free biomolecular probe because Cao et al. demonstrates that metal colloids (i.e. nanoparticles) are useful in signal enhancement of SERS assays and allow for the detection of multiple targets in one assay (pg.1537), and further demonstrates the benefits of using such assays to detect *B. anthracis*. The skilled artisan would have had a reasonable expectation of success in detecting *B. anthracis* and further including a metal colloid attached to the free biomolecular probe in the method of Vo-Dinh et al. for signal enhancement and multiplexing capabilities. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed *B. anthracis* detection and metal colloid therein.

11. Claims 14, 27 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vo-Dinh (US 5,814,516) in view of Carron et al. (US 6,770,488 B1).

The teachings of Vo-Dinh are discussed above. This reference does not discuss the method and assay system wherein the fluorophore comprises Rhodamine B, rose bengal or fluorescein isothiocyanate.

The teachings of Carron et al. are discussed above, teaching the method and assay system for general use of analyte detection. Carron also discuss the fluorophore being fluorescein isothiocyanate (Example 5, col.17).

One of ordinary skill in the art would have been motivated to modify the method of Vo-Dinh et al. to use fluorescein isothiocyanate as the fluorophore because Carron demonstrates that such fluorophores were not only conventional in the art at the time of the invention for use in SERS assays, but are also beneficial to use in such methods and assays systems. The skilled artisan would have had a reasonable expectation of success in using fluorescein isothiocyanate in the method of Vo-Dinh et al. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed fluorescein isothiocyanate therein.

Summary

12. No claims are free of the prior art.
13. Malicka et al., "Effects of metallic silver particles on resonance energy transfer in labeled bovine serum albumin," Biochem. Biophys. Res. Comm., June 2002, Vol.294, pp.886-892, and Wohlstadter et al. (US 6,207,369) are noted as references of interest.

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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is 571-272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Molly E Baughman
Examiner
Art Unit 1637

MEB 9/30/07

Kenneth R. Horlick
KENNETH R. HORLICK, PH.D.
PRIMARY EXAMINER

10/1/07